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jc868 U.S. PTO 12/13/00

jc841 U.S. PTO 09/738859 12/13/00

Patent
Attorney's Docket No. 032740-005

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

UTILITY PATENT APPLICATION TRANSMITTAL LETTER

Box PATENT APPLICATION
Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

Enclosed for filing is the utility patent application of Dinesh Patel, Jeffrey W. Jacobs, Rakesh Jain, Zhi-Jie Ni and Zhengyu Yuan for NOVEL SUCCINATE COMPOUNDS, COMPOSITIONS AND METHODS OF USE AND PREPARATION.

[ ] Applicant(s) hereby request(s) that the above-captioned application **NOT BE PUBLISHED** under 35 U.S.C. § 122(b) and 37 C.F.R. § 1.211. The undersigned hereby certifies that the invention disclosed in this application has not and will not be the subject of an application filed in another country, or under a multilateral international agreement, that requires publication at eighteen months after filing.

[ ] Applicant(s) suggest(s) Figure _ for inclusion on the front page of the patent application publication and patent.

Also enclosed are:

[ ] ______ sheet(s) of [ ] formal [ ] informal drawing(s);

[ ] a claim for foreign priority under 35 U.S.C. §§ 119 and/or 365 is [ ] hereby made to _ filed in _ on _;

[ ] in the declaration;

[ ] a certified copy of the priority document;

[ ] a General Authorization for Petitions for Extensions of Time and Payment of Fees;

[ ] an Assignment document;

[ ] an Information Disclosure Statement;

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[X] Other: return postcard.

21839

(10/00)

[X] An [ ] executed [X] unexecuted declaration of the inventor(s)
[X] also is enclosed [ ] will follow.

[ ] Small entity status is hereby claimed.

[X] The filing fee has been calculated as follows:

CLAIMS					
	NO. OF CLAIMS		EXTRA CLAIMS	RATE	FEE
Basic Application Fee					$710.00 (101)
Total Claims	257	MINUS 20 =	237	× $18.00 (103) =	4,266.00
Independent Claims	1	MINUS 3 =	0	× $80.00 (102) =	0.00
If multiple dependent claims are presented, add $270.00 (104)					270.00
Total Application Fee					$5,246.00
If small entity status is claimed, subtract 50% of Total Application Fee					
Add Assignment Recording Fee $ if Assignment document is enclosed					
TOTAL APPLICATION FEE DUE		****FEE NOT INCLUDED****			**$5,246.00**

[X] This application is being filed without a filing fee. Issuance of a Notice to File Missing Parts of Application is respectfully requested.

[ ] A check in the amount of $ _________ is enclosed for the fee due.

[ ] Charge $ _________ to Deposit Account No. 02-4800 for the fee due.

Please address all correspondence concerning the present application to:

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Respectfully submitted,

BURNS, DOANE, SWECKER & MATHIS, L.L.P.

Date: December 13, 2000

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PATENT
Attorney Docket No. 032740-005

BE IT KNOWN, that We, Dinesh Patel, Jeffrey W. Jacobs, Rakesh Jain, Zhi-Jie Ni and Zhengyu Yuan respectively of Fremont, California; San Mateo, California; Fremont, California; Fremont, California; and Fremont, California have invented new and useful improvements in:

NOVEL SUCCINATE COMPOUNDS, COMPOSITIONS AND METHODS OF USE AND PREPARATION

NOVEL SUCCINATE COMPOUNDS, COMPOSITIONS AND METHODS OF USE AND PREPARATION

CROSS-REFERENCE TO RELATED APPLICATIONS

The application claims priority under 35 U.S.C. 119(e) to U.S. Provisional Application Serial No. 60/---,---, which was converted pursuant to 37 C.F.R. § 1.53(b)(2)(ii) from U.S, Patent Application No. 09/466,402, filed on December 17, 1999, the disclosure of which is incorporated herein in its entirety.

BACKGROUND OF THE INVENTION

Field of the invention

This invention is directed to novel succinate compounds. This invention is also directed to uses of these compounds in various medicinal applications, including treating disorders amenable to treatment by peptidyl deformylase inhibitors. This invention is still further directed to pharmaceutical compounds comprising these compounds and methods of synthesis thereof.

State of the Art

Treatment of microbial infection in host organisms requires an effective means to kill the microbe while doing as little harm to the host as possible. Accordingly, agents which target characteristics unique to a pathology-causing microorganism are desirable for treatment. Penicillin is an extremely well known example of such an agent. Penicillin acts by inhibiting biosynthesis of bacterial cell walls. Since mammalian cells do not require cell walls for survival, administration of penicillin to a human infected with bacteria can kill the bacteria without killing human cells.

However, the use of antibiotics and antimicrobials has also resulted in increased resistance to these agents. As bacteria become resistant to older, more widely used antimicrobial agents, new antimicrobials must be developed in order to provide effective treatments for human and non-human animals suffering from microbial infection.

Peptide deformylase is a metallopeptidase found in prokaryotic organisms such as bacteria. Protein synthesis in prokaryotic organisms begins with N-formyl methionine (fMet). After initiation of protein synthesis, the formyl group is removed

by the enzyme peptide deformylase (PDF); this activity is essential for maturation of proteins. It has been shown that PDF is required for bacterial growth (Chang et al. *J. Bacteriol.* 171:4071-4072 (1989); Meinnel T, Blanquet S, *J. Bacteriol.* 176(23):7387-90 (1994); Mazel D et al., *EMBO J.* 13(4):914-23 (1994)). Since protein synthesis in eukaryotic organisms does not depend on fMet for initiation, agents that will inhibit PDF are attractive candidates for development of new antimicrobial and antibacterial drugs. Prokaryotic organisms, including disease-causing prokaryotes, are described in Balows, A., H.G. Truper, M. Dworkin, W. Harder, and K.-H. Schleifer (eds.), *The Prokaryotes*, 2nd ed., New York: Springer-Verlag, 1992; and Holt, J.G. (editor-in-chief). *Bergey's Manual of Systematic Bacteriology*, Vols. 1-4, Baltimore: Williams & Wilkins, 1982, 1986, 1989.

PDF is part of the metalloproteinase superfamily. While PDF clearly shares many of the features which characterize metalloproteinases, it differs from other members of the superfamily in several important respects. First, the metal ion in the active enzyme appears to be Fe (II), or possibly another divalent cationic metal, instead of the zinc ion more commonly encountered. Rajagopalan *et al.*, *J. Am. Chem. Soc.*, 119:12418-19 (1997). Second, the divalent ion appears to play an important role, not only in catalysis, but also in the structural integrity of the protein. Third, the third ligand of the divalent ion is a cysteine, rather than a histidine or a glutamate, as in other metalloproteinases and is not located at the C-terminal side of the HEXXH motif but far away along the amino acid sequence and N-terminal to the motif. Finally, the solution structure shows significant differences in the secondary and tertiary structure of PDF compared to other prototypical metalloproteinases *see* Meinnel et al. *J. Mol. Biol.* 262:375-386 (1996). PDF from *E. coli*, *Bacillus stearothermophilus*, and *Thermus thermophilus* have been characterized *see* Meinnel et al., *J Mol Biol* 267:749-761 (1997). The enzyme studied by Meinnel et al. contained a zinc ion as the divalent ion and the structural features summarized above were obtained from zinc-containing proteins. The structure of the protein has also been determined by NMR (*see* O'Connell *et al.*, *J. Biomol. NMR* 13(4):311-24 (1999)).

Metalloproteinases are critical to many aspects of normal metabolism. The class known as matrix metalloproteinases (MMPs) are involved in tissue remodeling, such as degradation of the extracellular matrix. These enzymes are believed to play a role in normal or beneficial biological events such as the formation of the corpus

luteum during pregnancy (*see* Liu *et al., Endocrinology* 140(11):5330-8 (1999)), wound healing (Yamagiwa *et al.*, *Bone* 25(2):197-203 (1999)), and bone growth in healthy children (Bord et al., *Bone* 23(1):7-12 (1998)). Disorders involving metalloproteinases have been implicated in several diseases such as cancer, arthritis, and autoimmune diseases.

Because of the importance of MMPs in normal physiological processes, it would be preferable to develop agents that inhibit PDF, a metalloproteinase present only in prokaryotes, while avoiding significant inhibition of MMPs. Alternatively, PDF inhibitors which also inhibit MMPs can be of use where the therapeutic benefits of inhibiting PDF outweigh the risk of side effects from MMP inhibition.

A wide variety of compounds have been developed as candidate inhibitors of MMPs and other metalloproteinases, and much effort has also been directed at synthetic methods for these compounds and related compounds. *See* Izquierdo-Martin et al. (1992) *J. Am. Chem. Soc.* 114:325-331; Cushman et al. (1981) Chapter 5 "*Specific Inhibitors of Zinc Metallopeptidases*" in *Topics in Molecular Pharmacology* (Burgen & Roberts, eds.); Mohler et al. *Nature* 370:218-220 (1994); Gearing et al., *Nature* 370:555-557 (1994); McGeehan et al., *Nature* 370:558-561 (1994); U.S. Patent Nos. 4,052,511, 4,303,662, 4,311,705, 4,321,383, 4,599,361, 4,804,676, 5,128,346, 5,256,657, 5,268,384, 5,447,929, 5,453,423, 5,552,419, 5,614,625, 5,643,908, 5,712,300, and 5,869,518; European patent publications EP 236872, EP 274453, EP 334244, EP 423943, EP 489577, EP 489579, EP 497192, EP 574758; and International PCT Patent Applications Publication Nos. WO 90/05716, WO 90/05719, WO 91/02716, WO 92/13831, WO 92/22523, WO 93/09090, WO 93/09097, WO 93/20047, WO 93/24449, WO 93/24475, WO 94/02446, WO 94/02447, WO 94/21612, WO 94/25434, WO 94/25435, WO 95/33731, WO 96/25156, WO 96/26918 WO 97/30707, WO 97/49674, WO 98/55449, and WO 99/02510.

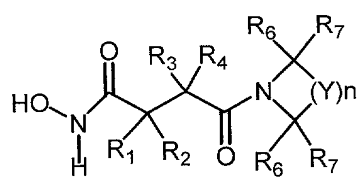
Research on inhibitors of PDF is much less extensive than that for inhibitors of MMPs. N-formyl hydroxylamine derivatives are described in International Patent Application WO 99/39704. Peptide aldehyde inhibitors of PDFs are described in Durand *et al., Arch. Biochem. Biophys.*, 367(2):297-302 (1999). The PDF inhibitor (S)-2-O-(H-phosphonoxy)-L-caproyl-L-leucyl-p-nitroanilide is described in Hao *et al., Biochemistry* 38:4712-4719 (1999), and peptidyl H-phosphonate inhibitors of PDF are discussed in Hu *et al., Bioorg. Med. Chem. Lett.* 8:2479-2482 (1998).

Formylated peptides and pseudopeptides are described in Meinnel *et al.*, *Biochemistry* 38(14):4288-4295 (1999) as inhibitors of PDF.

In view of the importance of identifying new antibiotics to treat bacteria resistant to existing antibiotics, and the relatively small amount of work that has been carried out on PDF inhibitors, it is desirable to develop novel inhibitors of PDF for evaluation and use as antibacterial and antimicrobial agents. The present invention fulfills this need.

SUMMARY OF THE INVENTION

In one aspect, this invention is directed to a compound of Formula (I):



wherein:

R_1 is hydrogen, halo, -OH, $-R_8OR_9$, $-R_9$, $-OR_9$, -SH, $-SR_9$, $-NH_2$, $-NHR_9$ $-NR_9R_{10}$, -NHC(=O)H, $-NR_9C(=O)H$, $-NHC(=O)R_9$, $-NR_9C(=O)R_{10}$, $-NHC(=O)NH_2$, $-NR_9C(=O)NH_2$, $-NHC(=O)NHR_9$, $-NHC(=O)NR_9R_{10}$, $-NR_9C(=O)NR_{9a}R_{10}$, $-NHC(=O)OR_9$, $-NR_9C(=O)OR_{10}$, $-NHS(=O)_2R_9$, $-NR_9S(=O)_2R_{10}$, $-NHS(=O)_2OR_9$, or $-NR_9S(=O)_2OR_{10}$ where R_8 is selected from the group consisting of $-C_1-C_{12}$ alkylene, substituted alkylene, or heteroalkylene, $-C_1-C_{12}$ alkenylene, substituted alkenylene, or heteroalkenylene, $-C_1-C_{12}$ alkynylene, substituted alkynylene, or heteroalkynylene, and $-(C_1-C_8$ alkylene or substituted alkylene$)_{n1}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n2}$ where n1 and n2 are independently 0 or 1; and R_9, R_{9a} and R_{10} are independently selected from the group consisting of $-C_1-C_{12}$ alkyl, substituted alkyl, or heteroalkyl, $-C_1-C_{12}$ alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1-C_{12}$ alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1-C_8$ alkyl or substituted alkyl$)_{n3}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n4}$ where n3 and n4 are independently 0 or 1;

R_2 is independently hydrogen or $-R_9$ wherein R_9 is as defined above;

R_3 is hydrogen, halo, $-R_{11}$, -OH, $-OR_{11}$, $-R_{12}OR_{11}$, -SH, $-SR_{11}$, $-NH_2$, $-NHR_{11}$, $-NR_{11}R_{13}$, -NHC(=O)H, $-NR_{11}C(=O)H$, $-NHC(=O)R_{11}$, $-NR_{11}C(=O)R_{13}$, $-NHC(=O)NH_2$, $-NR_{11}C(=O)NH_2$, $-NHC(=O)NHR_{11}$, $-NHC(=O)NR_{11}R_{13}$,

$-NR_{11}C(=O)NR_{11a}R_{13}$, $-NHC(=O)OR_{11}$, $-NR_{11}C(=O)OR_{13}$, $-NHS(=O)_2R_{13}$, $-NR_{11}S(=O)_2R_{13}$, $-NHS(=O)_2OR_{11}$, or $-NR_{11}S(=O)_2OR_{13}$, where R_{12} is selected from the group consisting of $-C_1$-C_{12} alkylene, substituted alkylene, or heteroalkylene, $-C_1$-C_{12} alkenylene, substituted alkenylene, or heteroalkenylene, $-C_1$-C_{12} alkynylene, substituted alkynylene, or heteroalkynylene, and $-(C_1$-C_8 alkylene or substituted alkylene$)_{n5}$-$(C_3$-C_{12} arylene or heteroarylene$)$-$(C_1$-C_8 alkyl or substituted alkyl$)_{n6}$ where n5 and n6 are independently 0 or 1; and R_{11}, R_{11a} and R_{13} are independently selected from the group consisting of $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n7}$-$(C_3$-C_{12} arylene or heteroarylene$)$-$(C_1$-C_8 alkyl or substituted alkyl$)_{n8}$ where n7 and n8 are independently 0 or 1;

R_4 is hydrogen or $-R_{11}$ where $-R_{11}$ is as defined above;

n is an integer from 1 to 5;

zero or one Y is selected from the group consisting of -O-, $-NR_{11}$- where R_{11} is as defined above, and -S-, and all remaining Y are $-CR_6R_7$- where R_6 and R_7 are each independently selected from the group consisting of hydrogen, $-R_{14}$, -OH, $-OR_{14}$, -SH, $-SR_{14}$, $-NH_2$, $-NHR_{14}$, $-NR_{14}R_{15}$, -C(=O)H, $-C(=O)R_{14}$, $-C(=O)NH_2$, $-C(=O)NHR_{14}$, $-C(=O)NR_{14}R_{15}$, -C(=O)OH, $-C(=O)OR_{14}$, -C(=O)SH, $-C(=O)SR_{14}$, $-C(=O)CH_3$, $-C(=O)CH_2R_{14}$, $-C(=O)CHR_{14}R_{15}$, $-C(=O)CR_{14}R_{15}R_{16}$, $-C(=O)OCH_3$, $-C(=O)OCH_2R_{14}$, $-C(=O)OCHR_{14}R_{15}$, $-C(=O)OCR_{14}R_{15}R_{16}$, $-S(=O)_2NH_2$, $-S(=O)_2NHR_{14}$, $-S(=O)_2NR_{14}R_{15}$, -NHC(=O)H, $-N(R_{14})C(=O)H$, $-NHC(=O)R_{15}$, $-N(R_{14})C(=O)R_{15}$, $-NHC(=O)OR_{14}$, $-NHS(=O)_2H$, $-N(R_{14})S(=O)_2H$, $-NHS(=O)_2OR_{15}$, $-N(R_{14})S(=O)_2OR_{15}$, $-N(H)S(=O)_2R_{15}$, $-N(R_{14})S(=O)_2R_{15}$ and where two vicinal R_6 or R_7 groups combine to form a substituted or unsubstituted $-C_4$-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group where R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of $-C_1$-C_{12} alkyl, substituted alkyl, or heteroalkyl, $-C_1$-C_{12} alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1$-C_{12} alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, and $-(C_1$-C_8 alkyl or substituted alkyl$)_{n9}$-$(C_3$-C_{12} arylene or heteroarylene$)$-$(C_1$-C_8 alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1; or when R_{14} and R_{15} are attached to a nitrogen atom they can combine to form a substituted or unsubstituted $-C_4$-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; or

a pharmaceutically acceptable salt thereof.

Preferably the compound of Formula (I) inhibits peptidyl deformylase at an IC_{50} of less than or equal to about 100 nm, preferably of less than or equal to 10 nm, more preferably of less than or equal to 1 nm.

Preferably the compound of Formula (I) displays a selectivity for peptidyl deformylase over at least one metalloproteinase selected from the group consisting of ACE and Matrilysin of greater than or equal to about 10 times, more preferably of greater than or equal to about 100 times, still more preferably of greater than or equal to about 1000 times.

In a second aspect, this invention is directed to pharmaceutical compositions comprising a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient.

In a third aspect, this invention is directed to a method of treatment of a disease in a mammal treatable by administration of a peptidyl deformylase inhibitor which method comprises administration of a therapeutically effective amount of a pharmaceutical composition comprising a therapeutically effective amount of a compound of Formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable excipient either alone or in combination with other pharmacologically active agents. In particular, the compounds of this invention are useful in treating microbial diseases. The microbial infection can be due to bacteria, other prokaryotes, or other organisms, including parasites, dependent on peptide deformylase for growth or survival.

In a fourth aspect, this invention is directed to the use of a compound of Formula (I) or a pharmaceutically acceptable salts thereof in the preparation of a medicament for use in the treatment of diseases mediated by peptidyl deformylase enzyme.

In a fifth aspect, this invention is directed to a method for identifying compounds useful in treating microbial infections, comprising performing an assay to identify compounds which meet the criterion of either i) an IC_{50} for peptide deformylase of less than or equal to about 1 μM, or ii) an MIC for a disease-causing pathogen of less than or equal to about 32 μg/ml; performing an assay to identify compounds which meet the criterion of iii) displaying a selectivity for peptide deformylase over at least one metalloproteinase selected from the group consisting of Angiotensin Converting Enzyme (ACE) and Matrilysin of greater than or equal to about 10 times; and selecting compounds which meet either both criteria i) and iii), or

both criteria ii) and iii). More preferably, the compounds so identified meet the criterion of either i) an IC_{50} for peptide deformylase of less than or equal to about 100 nM, or ii) an MIC for a disease-causing pathogen of less than or equal to about 10 μg/ml.

DETAILED DESCRIPTION OF THE INVENTION

Unless otherwise stated, the following terms as used in the specification have the following meaning.

The term "alkyl" refers to saturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms. Examples of alkyl groups include, but are not limited to, groups such as methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, t-butyl, n-pentyl, neopentyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclobutylmethyl, cyclobutylethyl, cyclopentylmethyl, cyclopentylethyl, and adamantyl. Cyclic alkyl groups can consist of one ring, including, but not limited to, groups such as cycloheptyl, or multiple fused rings, including, but not limited to, groups such as adamantyl or norbornyl.

The term "alkylene" means a saturated divalent aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms, e.g., methylene, ethylene, 2,2-dimethylethylene, propylene, 2-methyl-propylene, butylene, pentylene, cyclopentylmethylene, and the like.

The term "substituted alkyl" means an alkyl group as defined above that is substituted with one or more substituents, preferably one to three substituents selected from the group consisting of halogen (fluoro, chloro, bromo, and iodo, preferably fluoro, chloro, or bromo), alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. The phenyl group may optionally be substituted with one to three substituents selected from the group consisting of halogen (fluoro, chloro, bromo, and iodo, preferably fluoro, chloro, or bromo), alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide. Examples of substituted alkyl groups include, but are

not limited to, $-CF_3$, $-CF_2-CF_3$, hydroxymethyl, 1- or 2-hydroxyethyl, methoxymethyl, 1- or 2-ethoxyethyl, carboxymethyl, 1- or 2- carboxyethyl, methoxycarbonylmethyl, 1- or 2-methoxycarbonyl ethyl, benzyl, and the like.

The term "substituted alkylene" means an alkylene group as defined above that is substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of halogen (fluoro, chloro, bromo, and iodo, preferably fluoro, chloro, or bromo), alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. The phenyl group may optionally be substituted with one to three substituents selected from the group consisting of halogen (fluoro, chloro, bromo, and iodo, preferably fluoro, chloro, or bromo), alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide. Examples of substituted alkyl groups include, but are not limited to, $-CF_2-$, $-CF_2-CF_2-$, hydroxymethylene, 1- or 2-hydroxyethylene, methoxymethylene, 1- or 2-ethoxyethylene, carboxymethylene, 1- or 2-carboxy-ethylene, and the like.

The term "alkenyl" refers to unsaturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms, which contain at least one double bond (-C=C-). Examples of alkenyl groups include, but are not limited to, allyl vinyl, $-CH_2-CH=CH-CH_3$, $-CH_2-CH_2$-cyclopentenyl and $-CH_2-CH_2$-cyclohexenyl where the ethyl group can be attached to the cyclopentenyl, cyclohexenyl moiety at any available carbon valence.

The term "alkenylene" refers to unsaturated divalent aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms, which contain at least one double bond (-C=C-). Examples of alkenylene groups include, but are not limited to, -CH=CH-, $-CH_2-CH=CH-CH_2-$, $-CH_2-CH$(cyclopentenyl)- and the like.

The term "alkynyl" refers to unsaturated aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms,

which contain at least one triple bond (-C≡C-). Examples of alkynyl groups include, but are not limited to, acetylene, 2-butynyl, and the like.

The term "alkynylene" refers to unsaturated divalent aliphatic groups including straight-chain, branched-chain, cyclic groups, and combinations thereof, having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms, which contain at least one triple bond (-C≡C-). Examples of alkynylene groups include, but are not limited to, -C≡C-, -C≡C-CH_2-, and the like.

The term "substituted alkenyl" or "substituted alkynyl," refers to the alkenyl and alkynyl groups as defined above that are substituted with one or more substituents, selected from the group consisting of halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. Examples of substituted alkenyl and alkynyl groups include, but are not limited to, -CH=CF_2, hydroxyethenyl, methoxypropenyl, hydroxypropynyl, and the like.

The term "substituted alkenylene" or "substituted alkynylene," refers to the alkenylene and alkynylene groups as defined above that are substituted with one or more substituents, selected from the group consisting of halogen, alkoxy, acyloxy, amino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group.

The term "aryl" or "Ar" refers to an aromatic carbocyclic group of 6 to 14 carbon atoms having a single ring (including, but not limited to, groups such as phenyl) or multiple condensed rings (including, but not limited to, groups such as naphthyl or anthryl), and includes both unsubstituted and substituted aryl groups. Substituted aryl is an aryl group that is substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, halogen, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, aryloxy, benzyl, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group.

Representative examples include, but are not limited to, naphthyl, phenyl, chlorophenyl, iodophenyl, methoxyphenyl, carboxyphenyl, and the like.

The term "arylene" refers to the diradical derived from aryl (including substituted aryl) as defined above and is exemplified by 1,2-phenylene, 1,3-phenylene, 1,4-phenylene, 1,2-naphthylene and the like.

The term "amino" refers to the group $-NH_2$.

The term "thioalkoxy " means a radical -SR where R is an alkyl as defined above e.g., methylthio, ethylthio, propylthio, butylthio, and the like.

The term "mono and "dialkylamino" means a radical –NHR and -NRR' respectively where R and R' independently represent an alkyl group as defined herein. Representative examples include, but are not limited to dimethylamino, methylethylamino, di(1-methylethyl)amino, (cyclohexyl)(methyl)amino, (cyclohexyl)(ethyl)amino, (cyclohexyl)(propyl)amino, (cyclohexylmethyl)(methyl)-amino, (cyclohexylmethyl)(ethyl)amino, and the like.

The term "acyloxy" means a radical –OC(O)R, where R is hydrogen, alkyl, aryl, heteroaryl or substituted alkyl wherein alkyl, aryl, heteroaryl, and substituted alkyl are as defined herein. Representative examples include, but are not limited to formyl, acetyloxy, cylcohexylcarbonyloxy, cyclohexylmethylcarbonyloxy, benzoyloxy, benzylcarbonyloxy, and the like.

The term "heteroalkyl," "heteroalkenyl," and "heteroalkynyl" refers to alkyl, alkenyl, and alkynyl groups respectively as defined above, that contain the number of carbon atoms specified (or if no number is specified, having 1 to 12 carbon atoms) which contain one or more heteroatoms, preferably one to three heteroatoms, as part of the main, branched, or cyclic chains in the group. Heteroatoms are independently selected from the group consisting of –NR-, -NRR, (where each R is hydrogen or alkyl), -S-, -O-, -SR (R is hydrogen or alkyl), -OR (R is hydrogen or alkyl), and P; preferably –NR where R is hydrogen or alkyl and/or O. Heteroalkyl, heteroalkenyl, and heteroalkynyl groups may be attached to the remainder of the molecule either at a heteroatom (if a valence is available) or at a carbon atom. Examples of heteroalkyl groups include, but are not limited to, groups such as $-O-CH_3$, $-CH_2-O-CH_3$, $-CH_2-CH_2-O-CH_3$, $-S-CH_2-CH_2-CH_3$, $-CH_2-CH(CH_3)-S-CH_3$, $-CH_2-CH_2-NH-CH_2-CH_3$, 1-ethyl-6-propylpiperidino, 2-ethylthiophenyl, piperazino, pyrrolidino, piperidino, morpholino, and the like. Examples of heteroalkenyl groups

include, but are not limited to, groups such as -$CH=CH-NH-CH(CH_3)-CH_3$, and the like.

The term “carboxaldehyde” means –CHO.

The term “ carboalkoxy” means –C(O)OR where R is alkyl as defined above and include groups such as methoxycarbonyl, ethoxycarbonyl, and the like.

The term “carboxamide” means –C(O)NHR or –C(O)NRR’where R and R’ are independently hydrogen or alkyl as defined above. Representative examples include groups such as aminocarbonyl, methylaminocarbonyl, dimethylaminocarbonyl, and the like.

The term “heteroaryl” or “HetAr” refers to an aromatic carbocyclic group of 3 to 9 ring atoms forming a single ring and having at least one hetero atom, preferably one to three heteroatoms including, but not limited to, heteroatoms such as N, O, P, or S, within the ring. Representative examples include, but are not limited to single ring such as imidazolyl, pyrazolyl, pyrazinyl, pyridazinyl, pyrimidinly, pyrrolyl, pyridyl, thiophene, and the like, or multiple condensed rings such as indolyl, quinoline, quinazoline, benzimidazolyl, indolizinyl, benzothienyl, and the like.

The heteroalkyl, heteroalkenyl, heteroalkynyl and heteroaryl groups can be unsubstituted or substituted with one or more substituents, preferably one to three substituents, selected from the group consisting of alkyl, alkenyl, alkynyl, benzyl, halogen, alkoxy, acyloxy, amino, mono or dialkylamino, hydroxyl, mercapto, carboxy, benzyloxy, phenyl, aryloxy, cyano, nitro, thioalkoxy, carboxaldehyde, carboalkoxy and carboxamide, or a functionality that can be suitably blocked, if necessary for purposes of the invention, with a protecting group. Examples of such substituted heteroalkyl groups include, but are not limited to, piperazine, pyrrolidine, morpholine, or piperidine, substituted at a nitrogen or carbon by a phenyl or benzyl group, and attached to the remainder of the molecule by any available valence on a carbon or nitrogen, -$NH-SO_2$-phenyl, -NH-(C=O)O-alkyl, -NH-(C=O)O-alkyl-aryl, and the like. The heteroatom(s) as well as the carbon atoms of the group can be substituted. The heteroatom(s) can also be in oxidized form.

The term “heteroarylene” refers to the diradical group derived from heteroaryl (including substituted heteroaryl), as defined above, and is exemplified by the groups 2,6-pyridylene, 2,4-pyridinylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridnylene, 2,5-indolenyl, and the like.

The term “heteroalkylene”, “heteroalkenylene”, and “heteroalkynylene” refers to the diradical group derived from heteroalkyl, heteroalkenyl, and heteroalkynyl (including substituted heteroalkyl, heteroalkenyl, and heteroalkynyl), as defined above.

The term "alkylaryl" refers to an alkyl group having the number of carbon atoms designated, appended to one, two, or three aryl groups.

The term “alkoxy” as used herein refers to an alkyl, alkenyl, or alkynyl linked to an oxygen atom and having the number of carbon atoms specified, or if no number is specified, having 1 to 12 carbon atoms. Examples of alkoxy groups include, but are not limited to, groups such as methoxy, ethoxy, *tert*-butoxy, and allyloxy.

The term “aryloxy” as used herein refers to an aryl group linked to an oxygen atom at one of the ring carbons. Examples of alkoxy groups include, but are not limited to, groups such as phenoxy, 2-, 3-, or 4-methylphenoxy, and the like.

The term "halogen" as used herein refer to Cl, Br, F or I substituents, preferably fluoro or chloro.

The term “-(C_1-C_{12}) alkyl, substituted alkyl, or heteroalkyl” means an alkyl, substituted alkyl or heteroalkyl group respectively as defined above and having 1 to 12 carbon atoms. For example, when R_1 is -(C_1-C_{12}) alkyl, substituted alkyl, or heteroalkyl it means that R_1 can be -(C_1-C_{12}) alkyl or -(C_1-C_{12})substituted alkyl, or -(C_1-C_{12})heteroalkyl.

The term “-(C_1-C_{12}) alkenyl, substituted alkenyl, or heteroalkenyl” means an alkenyl, substituted alkenyl, or heteroalkenyl group as defined above and having 1 to 12 carbon atoms.

The “-(C_1-C_{12}) alkynyl, substituted alkynyl, or heteroalkynyl” means an alkynyl, substituted alkynyl, or heteroalkynyl group as defined above and having 1 to 12 carbon atoms.

The term “-(C_1-C_{12}) alkylene, substituted alkylene, or heteroalkylene” means an alkylene, substituted alkylene, or heteroalkylene group as defined above and having1 to 12 carbon atoms.

The term “-(C_1-C_{12}) alkenylene, substituted alkenylene, or heteroalkenylene” means that the alkenylene, substituted alkenylene, or heteroalkenylene group as defined above and having 1 to 12 carbon atoms.

The term " -(C_1-C_{12}) alkynylene, substituted alkynylene, or heteroalkynylene" means an alkynylene, substituted alkynylene, or heteroalkynylene group as defined above and having 1 to 12 carbon atoms.

The term "and -(C_1-C_8 alkylene or substituted alkylene)$_{n5}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n6}$ where n5 and n6 are independently 0 or 1" means that "when n5 and/or n6 are 0 then -(C_1-C_8 alkylene or substituted alkylene)$_{n5}$ and/or -(C_1-C_8 alkylene or substituted alkylene)$_{n6}$" are a covalent bond or when n5 and/or n6 are 1, then the alkylene or substituted alkylene group is present and can have 1 to 8 carbon atoms. The term -(C_3-C_{12} arylene or heteroarylene)- means that the arylene has 6 to 12 carbon atoms (e.g., phenylene, naphtylene, and the like) and heteroarylene groups have 3 to 12 carbons atoms and additionally contain one to three heteroatoms including, but not limited to, heteroatoms such as N, O, P, or S, within the ring (e.g., 2,6-pyridylene, 2,4-pyridinylene, 1,2-quinolinylene, 1,8-quinolinylene, 1,4-benzofuranylene, 2,5-pyridylene, 2,5-indolenyl, and the like) in accordance with the definition of the heteroarylene above. Additionally, it will be recognized by a person skilled in the art that when "-(C_1-C_8 alkylene or substituted alkylene)- " and "-(C_1-C_8 alkyl or substituted alkyl)- " are a covalent bond then -(C_3-C_{12} arylene or heteroarylene)- is an aryl or heteroaryl group as defined above.

"Protecting group" refers to a chemical group that exhibits the following characteristics: 1) reacts selectively with the desired functionality in good yield to give a protected substrate that is stable to the projected reactions for which protection is desired; 2) is selectively removable from the protected substrate to yield the desired functionality; and 3) is removable in good yield by reagents compatible with the other functional group(s) present or generated in such projected reactions. Examples of suitable protecting groups can be found in Greene et al. (1991) *Protective Groups in Organic Synthesis*, 2nd Ed. (John Wiley & Sons, Inc., New York). Preferred amino protecting groups include, but are not limited to, benzyloxycarbonyl (CBz), t-butyl-oxycarbonyl (Boc), t-butyldimethylsilyl (TBDIMS), 9-fluorenylmethyl-oxycarbonyl (Fmoc), or suitable photolabile protecting groups such as 6-nitroveratryloxy carbonyl (Nvoc), nitropiperonyl, pyrenylmethoxycarbonyl, nitrobenzyl, dimethyl dimethoxybenzil, 5-bromo-7-nitroindolinyl, and the like. Preferred hydroxyl protecting groups include Fmoc, TBDIMS, photolabile protecting groups (such as nitroveratryl oxymethyl ether (Nvom)), Mom (methoxy methyl ether), and Mem (methoxy ethoxy methyl ether). Particularly preferred protecting groups include

NPEOC (4-nitrophenethyloxycarbonyl) and NPEOM (4-nitrophenethyloxy-methyloxycarbonyl).

"Inhibitor" refers to a compound that interferes with the interaction between a target and its respective substrate(s) or endogenous ligand(s). Target molecules include, but are not limited to, enzymes and receptors. Enzyme inhibitors have been extensively studied from kinetic and mechanistic standpoints; *see, e.g.*, Fersht, A., *Enzyme Structure and Mechanism*, 2nd Ed., New York, W.H. Freeman, 1985. A useful measure of the effectiveness of a compound at inhibiting enzyme catalysis is the IC_{50} of that compound. The IC_{50} of a compound can determined by the equation

$$y = y_o/(1 + [In]/IC_{50})$$

where y is the measured reaction velocity, y_o is the reaction velocity in the absence of inhibitor, and [In] is the inhibitor concentration. Solving this equation at the inhibitor concentration [In] when $y = y_o/2$ yields IC_{50} of the inhibitor for the enzyme under study. Useful inhibitors have an IC_{50} equal to or less than about 10 TM, preferably equal to or less than about 1 TM. More preferably, the inhibitor has an IC_{50} equal to or less than about 100 nM, still more preferably equal to or less than about 10 nM, even more preferably equal to or less than about 1nM. Most preferably, inhibitors have an IC_{50} equal to or less than about 100 pM, or equal to or less than about 10 pM.

A selective inhibitor refers to an inhibitor that will inhibit the activity of one macromolecule, typically an enzyme, while exhibiting little or no inhibitory effect on another macromolecule, typically another enzyme. The compounds of the invention are particularly useful in that they display selective inhibition of peptidyl deformylase while exhibiting much lower inhibitory activity towards metalloproteinases such as matrilysin. The selectivity of an enzyme inhibitor can be indicated by dividing the IC_{50} of the compound for the enzyme which is not intended to be inhibited, by the IC_{50} of the compound for the enzyme which is intended to be inhibited. Thus, if a compound has an IC_{50} for matrilysin of 1 μM, and an IC_{50} for peptidyl deformylase of 0.01 μM, the compound displays a 100-fold (or 100 times) selectivity for peptidyl deformylase over matrilysin, or alternatively is said to be 100 times more selective for peptidyl deformylase compared to matrilysin. Useful compounds display a selectivity of greater than or equal to about 10 times, preferably greater than or equal to about 100 times, more preferably greater than or equal to about 1000 times, still more

preferably greater than or equal to about 10,000, for peptidyl deformylase over one or more other metalloproteinases, for example for peptidyl deformylase over matrilysin.

The compounds of the invention are intended for use in eukaryotic animals. Preferably, the animal is a vertebrate; more preferably, the animal is a mammal; most preferably, the animal is a human.

By "hydroxamic acid derivative," "hydroxamic acid derivative compound," "hydroxamic acid compound," "hydroxamate derivative," "hydroxamate derivative compound," or "hydroxamate compound" is meant any compound containing the functional group HN(OH)-C(=O)-.

Compounds that have the same molecular formula but differ in the nature or sequence of bonding of their atoms or the arrangement of their atoms in space are termed "isomers". Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and those that are non-superimposable mirror images of each other are termed "enantiomers". When a compound has an asymmetric center, for example, it is bonded to four different groups, a pair of enantiomers is possible. An enantiomer can be characterized by the absolute configuration of its asymmetric center and is described by the *R*- and *S*-sequencing rules of Cahn and Prelog, or by the manner in which the molecule rotates the plane of polarized light and designated as dextrorotatory or levorotatory (i.e., as (+) or (-)-isomers respectively). A chiral compound can exist as either individual enantiomer or as a mixture thereof. A mixture containing equal proportions of the enantiomers is called a "racemic mixture".

The compounds of this invention may possess one or more asymmetric centers; such compounds can therefore be produced as individual (*R*)- or (*S*)-stereoisomers or as mixtures thereof. For example, if the R_6 substituent in a compound of Formula (I) is 2-hydroxyethyl, then the carbon to which the hydroxy group is attached is an asymmetric center and therefore the compound of Formula (I) can exist as an (*R*)- or (*S*)-stereoisomer. Unless indicated otherwise, the description or naming of a particular compound in the specification and claims is intended to include both individual enantiomers and mixtures, racemic or otherwise, thereof. The methods for the determination of stereochemistry and the separation of stereoisomers are well-known in the art (*see* discussion in Chapter 4 of "Advanced Organic Chemistry", 4th edition J. March, John Wiley and Sons, New York, 1992).

A "pharmaceutically acceptable excipient" means an excipient that is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable, and includes an excipient that is acceptable for veterinary use as well as human pharmaceutical use. A "pharmaceutically acceptable excipient" as used in the specification and claims includes both one and more than one such excipient.

A "pharmaceutically acceptable salt" of a compound means a salt that is pharmaceutically acceptable and that possesses the desired pharmacological activity of the parent compound. Such salts include:

(1) acid addition salts, formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or formed with organic acids such as acetic acid, propionic acid, hexanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartaric acid, citric acid, benzoic acid, 3-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, mandelic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethane-disulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, 4-chlorobenzenesulfonic acid, 2-napthalenesulfonic acid, 4-toluenesulfonic acid, camphorsulfonic acid, 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynapthoic acid, salicylic acid, stearic acid, muconic acid, and the like; or

(2) salts formed when an acidic proton present in the parent compound either is replaced by a metal ion, e.g., an alkali metal ion, an alkaline earth ion, or an aluminum ion; or coordinates with an organic base such as ethanolamine, diethanolamine, triethanolamine, tromethamine, N-methylglucamine, and the like.

A compound of Formula (I) may act as a pro-drug. Prodrug means any compound which releases an active parent drug according to Formula (I) *in vivo* when such prodrug is administered to a mammalian subject. Prodrugs of a compound of Formula (I) are prepared by modifying functional groups present in the compound of Formula (I) in such a way that the modifications may be cleaved *in vivo* to release the parent compound. Prodrugs include compounds of Formula (I) wherein a hydroxy, amino, or sulfhydryl group in compound (I) is bonded to any group that may be cleaved *in vivo* to regenerate the free hydroxyl, amino, or sulfhydryl group, respectively. Examples of prodrugs include, but are not limited to esters (e.g., acetate,

formate, and benzoate derivatives), carbamates (e.g., N,N-dimethylamino-carbonyl) of hydroxy functional groups in compounds of Formula (I), and the like.

"Treating" or "treatment" of a disease includes:

(1) preventing the disease, i.e. causing the clinical symptoms of the disease not to develop in a mammal that may be exposed to or predisposed to the disease but does not yet experience or display symptoms of the disease,

(2) inhibiting the disease, i.e., arresting or reducing the development of the disease or its clinical symptoms, or

(3) relieving the disease, i.e., causing regression of the disease or its clinical symptoms.

A "therapeutically effective amount" means the amount of a compound that, when administered to a mammal for treating a disease, is sufficient to effect such treatment for the disease. The "therapeutically effective amount" will vary depending on the compound, the disease and its severity and the age, weight, etc., of the mammal to be treated.

PREFERRED EMBODIMENTS

While the broadest definition of this invention is set forth in the Summary of the Invention, certain compounds of Formula (I) are preferred. For example,

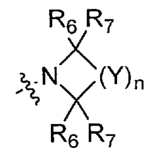
(A) (i) A preferred group of compounds is that wherein R_1 is hydrogen or hydroxy, preferably hydroxy. The stereochemistry at the carbon carrying the R_1 group is (*R*) or (*S*).

(ii) Another preferred group of compounds is that wherein R_1 is halo; preferably chloro or fluoro; more preferably fluoro. The stereochemistry at the carbon carrying the R_1 group is (*R*) or (*S*), preferably (*S*) when R_1 is fluoro.

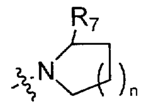
Within the above preferred groups, a more preferred group of compounds is that wherein R_2 and R_4 are hydrogen.

(iii) Yet another preferred group of compounds is that wherein R_3 is hydrogen or R_{11} where R_{11} is $-C_1$-C_{12} alkyl or $-(C_1$-C_8 alkylene$)_{n7}$-$(C_3$-C_{12} aryl or heteroaryl), preferably methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, 2-, 3-, 4-, or 5-methylpentyl, 4,4-dimethylbutyl, benzyl, 3-phenylpropyl, 2-phenylethyl, or 4-phenylbutyl, more preferably *n*-butyl. The stereochemistry at the carbon carrying the R_3 group is (*R*) or (*S*), preferably (*R*).

(iv) Yet another preferred group of compounds is that wherein the



group is a group of formula:



wherein:

n is 1 or 2, preferably 1; and

R_7 is:

(a) $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15} are independently selected from the group consisting of hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, and $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1; or R_{14} and R_{15} combine to form a substituted or unsubstituted $-(C_4-C_{10})$cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group.

Preferably, R_7 is $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15} are each independently hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, heteroaryl or R_{14} and R_{15}, when attached to the same carbon, combine to form a cyclic heteroalkyl, aryl or heteroaryl group.

More preferably, R_7 is $-C(=O)NHR_{15}$ where R_{15} is H or $-(C_1-C_{12})$ alkyl, aryl, or heteroaryl or $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15}form a substituted or unsubstituted $-(C_4-C_{10})$cyclic heteroalkyl.

Even more preferably R_7 is *n*-butylaminocarbonyl, *tert*-butylaminocarbonyl, benzylaminocarbonyl, 1,1-dimethylpropylaminocarbonyl, 2-(cyclohexen-1-yl)-ethylaminocarbonyl, indan-5-ylaminocarbonyl, 4,5-dimethylthiazol-2-ylamino-carbonyl, 4-phenoxyphenylaminocarbonyl, cyclopropylmethyl-aminocarbonyl, pyridin-2-ylaminocarbonyl, pyridin-3-ylaminocarbonyl, pyridin-4-ylmethylamino-carbonyl, morpholin-4-ylcarbonyl, 3,4-methylenedioxy-phenylaminocarbonyl, quinolin-3-ylaminocarbonyl, methylaminocarbonyl, 4-biphenylaminocarbonyl, 3-

phenoxyphenylaminocarbonyl, 3,4-dichlorophenyl-aminocarbonyl, 4-*tert*-butylphenylaminocarbonyl, 4-*tert*-butylaminocarbonyl, indan-2-ylaminocarbonyl, 2,2-dimethylpropylaminocarbonyl, 4-phenylthiazol-2-ylaminocarbonyl, 5-phenyl-thiadiazol-2-ylaminocarbonyl, 5-ethylthiadiazol-3-ylaminocarbonyl, thiadiazol-2-ylaminocarbonyl, 3-trifluoromethoxyphenyl-aminocarbonyl, 2,5-dimethylphenyl-aminocarbonyl, 2,5-dimethoxyphenylamino-carbonyl, 3,4-dichlorophenyl-aminocarbonyl, benzthiazol-2-ylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 2-hydroxybutylaminocarbonyl, 4-hydroxybutyl-aminocarbonyl, 1,4-benzodioxan-6-ylaminocarbonyl, isoquinolin-6-ylaminocarbonyl, methylaminocarbonyl, thiazol-2-yl-aminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 3-methylbutyl-aminocarbonyl, *n*-pentylaminocarbonyl, cyclohexylaminocarbonyl, 5-methylthiazol-2-ylamino-carbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 2,4-dimethoxyphenyl-aminocarbonyl, 3,4-methylenedioxyphen-5-yl-methylaminocarbonyl, allylaminocarbonyl, 2-methyl-allylaminocarbonyl, pyrrolidin-1-ylcarbonyl, ethylaminocarbonyl, phenylamino-carbonyl, indan-1-ylaminocarbonyl, 2-methoxyethylaminocarbonyl, indan-5-yl-aminocarbonyl, 3,4-difluorophenyl-aminocarbonyl, 5-methylisoxazol-5-yl-aminocarbonyl, 3-fluorophenylaminocarbonyl, 4-fluorophenylaminocarbonyl, *N*-methyl-*N*-phenylaminocarbonyl, 2-propylamino-carbonyl, 2-phenylpropyl-aminocarbonyl, *n*-propylaminocarbonyl, *N*-ethyl-*N*-(*n*-butyl)aminocarbonyl, benzylaminocarbonyl, thiazolidin-1-ylcarbonyl, piperazin-1-yl-carbonyl, piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, homopiperdin-1-ylcarbonyl, pyrimidin-2-ylamino-carbonyl, 4-methylpiperazin-1-ylcarbonyl, 4-methylpyrimidin-2-ylaminocarbonyl, pyrimidin-4-ylaminocarbonyl, pyrazin-2-ylaminocarbonyl, imidazol-2-ylamino-carbonyl.

In particular, R_7 is piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, pyrimidin-2-ylaminocarbonyl, or thiazol-2-ylaminocarbonyl.

More particularly, R_7 is piperidin-1-ylcarbonyl, azetidin-1-ylcarbonyl, ethylaminocarbonyl or thiazol-2-ylaminocarbonyl. The stereochemistry at the C2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*); or

(b) R_7 is $-NHC(=O)OR_{14}$ where R_{14} is hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or

-(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1.

Preferably, R_7 is -NHC(=O)OR_{14} where R_{14} is hydrogen or –(C_1-C_{12}) alkyl, alkoxy, aryl, heteroaryl; or

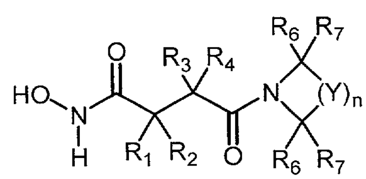
(c) R_7 is -C(=O)OR_{14} where R_{14} is hydrogen, -(C_1-C_{12}) alkyl, substituted alkyl, or heteroalkyl, -(C_1-C_{12}) alkenyl, substituted alkenyl, or heteroalkenyl, -(C_1-C_{12}) alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, or -(C_1-C_8 alkyl or substituted alkyl)$_{n9}$-(C_3-C_{12} arylene or heteroarylene)-(C_1-C_8 alkyl or substituted alkyl)$_{n10}$ where n9 and n10 are independently 0 or 1.

Preferably, R_7 is -C(=O)OR_{17} where R_{14} is hydrogen or –(C_1-C_{12}) alkyl, alkoxy, aryl, or heteroaryl.

More preferably, -C(=O)OR_{14} where R_{14} is alkyl, even more preferably R_7 is *tert*-butoxycarbonyl. The stereochemistry at the C_2 carbon atom of the pyrrolidine ring, i.e., carbon carrying the R_7 group is either (*R*) or (*S*), preferably (*S*).

The above defined embodiments of (i) - (iv) are employed either singularly or in any combination.

(B) Another preferred group of compounds is represented as Formula (IIa):



(IIa)

wherein:

R_1 is -OH, -OR_9, -R_8OR_9, -SH, -SR_9, -NH_2, -NHR_9 -N$R_9$$R_{10}$, -NHC(=O)H, -N$R_9$C(=O)H, -NHC(=O)$R_9$, -N$R_9$C(=O)$R_{10}$, -NHC(=O)N$H_2$, -N$R_9$C(=O)N$H_2$, -NHC(=O)NH$R_9$, -NHC(=O)N$R_9$$R_{10}$, -N$R_9$C(=O)N$R_{9a}$$R_{10}$, -NHC(=O)O$R_9$, -N$R_9$C(=O)O$R_{10}$, -NHS(=O)$_2$$R_9$, -N$R_9$S(=O)$_2$$R_{10}$, -NHS(=O)$_2OR_9$, or -N$R_9$S(=O)$_2OR_{10}$ where R_8 is selected from the group consisting of -C_1-C_{12} alkylene, -C_1-C_{12} alkenylene, and -C_1-C_{12} alkynylene and R_9, R_{9a} and R_{10} are independently

selected from the group consisting of $-C_1-C_{12}$ alkyl, $-C_1-C_{12}$ alkenyl, and $-C_1-C_{12}$ alkynyl;

R_2 is hydrogen or $-R_9$ where R_9 is as defined above;

R_3 is $-R_{11}$, -OH, $-OR_{11}$, $-R_{12}OR_{11}$, -SH, $-SR_{11}$, $-NH_2$, $-NHR_{11}$ $-NR_{11}R_{13}$, -NHC(=O)H, $-NR_{11}C(=O)H$, $-NHC(=O)R_{11}$, $-NR_{11}C(=O)R_{13}$, $-NHC(=O)NH_2$, $-NR_{11}C(=O)NH_2$, $-NHC(=O)NHR_{11}$, $-NHC(=O)NR_{11}R_{13}$, $-NR_{11}C(=O)NR_{11a}R_{13}$, $-NHC(=O)OR_{11}$, $-NR_{11}C(=O)OR_{13}$, $-NHS(=O)_2R_{13}$, $-NR_{11}S(=O)_2R_{13}$, $-NHS(=O)_2OR_{11}$, or $-NR_{11}S(=O)_2OR_{13}$, where R_{12} is selected from the group consisting of $-C_1-C_{12}$ alkylene, substituted alkylene, or heteroalkylene, $-C_1-C_{12}$ alkenylene, substituted alkenylene, or heteroalkenylene, $-C_1-C_{12}$ alkynylene, substituted alkynylene, or heteroalkynylene, and $-(C_1-C_8$ alkylene or substituted alkylene$)_{n5}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n6}$ where n5 and n6 are independently 0 or 1; and R_{11}, R_{11a}, and R_{13} are independently selected from the group consisting of $-C_1-C_{12}$ alkyl, substituted alkyl, or heteroalkyl, $-C_1-C_{12}$ alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1-C_{12}$ alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1-C_8$ alkyl or substituted alkyl$)_{n7}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n8}$ where n7 and n8 are independently 0 or 1;

R_4 is hydrogen or R_{11} where R_{11} is as defined above;

n is an integer from 1 to 5;

zero or one Y is selected from the group consisting of -O-, $-NR_{11}-$ where R_{11} is as defined above, and -S-, and all remaining Y are $-CR_6R_7-$ where R_6 and R_7 are each independently selected from the group consisting of hydrogen, $-R_{14}$, -OH, $-OR_{14}$, -SH, $-SR_{14}$, $-NH_2$, $-NHR_{14}$, $-NR_{14}R_{15}$, -C(=O)H, $-C(=O)R_{14}$, $-C(=O)NH_2$, $-C(=O)NHR_{14}$, $-C(=O)NR_{14}R_{15}$, -C(=O)OH, $-C(=O)OR_{14}$, -C(=O)SH, $-C(=O)SR_{14}$, $-C(=O)CH_3$, $-C(=O)CH_2R_{14}$, $-C(=O)CHR_{14}R_{15}$, $-C(=O)CR_{14}R_{15}R_{16}$, $-C(=O)OCH_3$, $-C(=O)OCH_2R_{14}$, $-C(=O)OCHR_{14}R_{15}$, $-C(=O)OCR_{14}R_{15}R_{16}$, $-S(=O)_2NH_2$, $-S(=O)_2NHR_{14}$, $-S(=O)_2NR_{14}R_{15}$, -NHC(=O)H, $-N(R_{14})C(=O)H$, $-NHC(=O)R_{15}$, $-N(R_{14})C(=O)R_{15}$, $-NHS(=O)_2H$, $-N(R_{14})S(=O)_2H$, $-NHS(=O)_2OR_{15}$, $-N(R_{14})S(=O)_2OR_{15}$, $-N(H)S(=O)_2R_{15}$, $-N(R_{14})S(=O)_2R_{15}$ and where two vicinal R_6 or R_7 groups combine to form a substituted or unsubstituted C_4-C_{10} cyclic alkyl, cyclic heteroalkyl, aryl or heteroaryl group; where R_{14}, R_{15} and R_{16} are each independently selected from the group consisting of $-C_1-C_{12}$ alkyl, substituted alkyl, or heteroalkyl,

$-C_1-C_{12}$ alkenyl, substituted alkenyl, or heteroalkenyl, $-C_1-C_{12}$ alkynyl, substituted alkynyl, or heteroalkynyl, and $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1; or a pharmaceutically acceptable salt thereof.

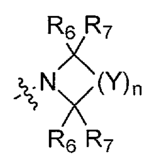
Within this group of compounds (IIa), a preferred group of compounds is that wherein the embodiments of (i) - (iv) defined below are employed either singularly or in any combination:

(i) A preferred group of compounds is that wherein R_1 is hydrogen or hydroxy and the stereochemistry at the carbon carrying the R_1 group is (*R*) or (*S*), preferably (*S*).

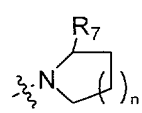
(ii) Another preferred group of compounds is that wherein R_2 and R_4 are hydrogen.

(iii) Another preferred group of compounds is that wherein R_3 is hydrogen or R_9 where R_9 is $-C_1-C_{12}$ alkyl or $-(C_1-C_8$ alkylene$)_{n7}-(C_3-C_{12}$ aryl or heteroaryl) where n7, preferably methyl, ethyl, *n*-propyl, *iso*-propyl, *n*-butyl, *iso*-butyl, *tert*-butyl, *n*-pentyl, *iso*-pentyl, *neo*-pentyl, *n*-hexyl, 2-, 3-, 4-, or 5-methylpentyl, 4,4-dimethylbutyl, benzyl, 3-phenylpropyl, 2-phenylethyl, or 4-phenylbutyl, more preferably *n*-butyl. The stereochemistry at the carbon carrying the R_3 group is (*R*) or (*S*), preferably (*R*).

(iv) Another preferred group of compounds is that wherein the



group is a group of formula:



wherein:

n is 1 or 2, preferably 1; and

R_7 is:

(a) $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15} are independently selected from the group consisting of hydrogen, $-(C_1-C_{12})$ alkyl, substituted alkyl, or heteroalkyl, $-(C_1-C_{12})$ alkenyl, substituted alkenyl, or heteroalkenyl, $-(C_1-C_{12})$ alkynyl, substituted alkynyl, or heteroalkynyl, alkoxy, and $-(C_1-C_8$ alkyl or substituted alkyl$)_{n9}-(C_3-C_{12}$ arylene or heteroarylene$)-(C_1-C_8$ alkyl or substituted alkyl$)_{n10}$ where n9 and n10 are independently 0 or 1.

Preferably, R_7 is $-C(=O)NR_{14}R_{15}$ where R_{14} and R_{15} are each independently hydrogen or $-(C_1-C_{12})$ alkyl, alkoxy, aryl, heteroaryl. More preferably, R_7 is $-C(=O)NHR_{15}$ where R_{15} is H or $-(C_1-C_{12})$ alkyl, aryl, or heteroaryl.

Even more preferably R_7 is *n*-butylaminocarbonyl, *tert*-butylaminocarbonyl, benzylaminocarbonyl, 1,1-dimethylpropylaminocarbonyl, 2-(cyclohexen-1-yl)-ethylaminocarbonyl, indan-5-ylaminocarbonyl, 4,5-dimethylthiazol-2-ylamino-carbonyl, 4-phenoxyphenylaminocarbonyl, cyclopropylmethylaminocarbonyl, pyridin-2-ylaminocarbonyl, pyridin-3-ylaminocarbonyl, pyridin-4-ylmethyl-aminocarbonyl, 3,4-methylenedioxyphenylaminocarbonyl, quinolin-3-ylaminocarbonyl, methylaminocarbonyl, 4-biphenylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 3,4-dichlorophenylaminocarbonyl, 4-*tert*-butylphenylaminocarbonyl, 4-*tert*-butylaminocarbonyl, indan-2-ylaminocarbonyl, 2,2-dimethylpropylaminocarbonyl, 4-phenylthiazol-2-ylaminocarbonyl, 5-phenylthiadiazol-2-ylaminocarbonyl, 5-ethylthiadiazol-3-ylaminocarbonyl, thiadiazol-2-ylaminocarbonyl, 3-trifluoromethoxyphenylaminocarbonyl, 2,5-dimethylphenylaminocarbonyl, 2,5-dimethoxyphenylamino-arbonyl, 3,4-dichlorophenylaminocarbonyl, benzthiazol-2-ylaminocarbonyl, 3-phenoxyphenylaminocarbonyl, 2-hydroxybutylaminocarbonyl, 4-hydroxybutyl-aminocarbonyl, 1,4-benzodioxan-6-ylaminocarbonyl, isoquinolin-6-ylaminocarbonyl, methylaminocarbonyl, thiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 3-methylbutylaminocarbonyl, *n*-pentylaminocarbonyl, cyclohexylaminocarbonyl, 5-methylthiazol-2-ylaminocarbonyl, 4-methylthiazol-2-yl-aminocarbonyl, 2,4-dimethoxyphenylaminocarbonyl, 3,4-methylenedioxyphen-5-yl-methylaminocarbonyl, allylaminocarbonyl, 2-methylallylaminocarbonyl, ethylaminocarbonyl, phenylaminocarbonyl, indan-1-ylaminocarbonyl, 2-methoxyethylaminocarbonyl, indan-5-ylaminocarbonyl, 3,4-difluorophenyl-aminocarbonyl, 5-methylisoxazol-5-ylaminocarbonyl, 3-fluorophenylaminocarbonyl,